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Editorial: probiotics in inflammatory bowel disease—wrong organisms, wrong disease, or flawed concepts?

When the number of meta-analyses and systematic reviews of any treatment approaches or exceeds that of primary research studies, it may be time to reconsider the entire concept or move on. The reanalysis by Derwa et al.[1] overcomes the limitations of previous reports over the past two decades, but the outcome is essentially the same—live microbes, referred to as probiotics, don't help patients with Crohn's disease and have limited impact on ulcerative colitis. Is this because we haven't tested the correct organisms, correct combination of organisms or the correct subsets of patients, or because of flawed concepts of host–microbe interactions in inflammatory bowel disease (IBD)?

The notion of using live microbes to treat IBD has always been intriguing, more because of implicit problems, conundrums and confusion than for any consistent benefit in humans.[2,3] The word probiotic(s) is imprecise and lends itself to the commonly mistaken assumption that all such organisms are equal. Collective terms of

convenience are a hindrance if they hide an essential truth. To avoid implicit bias within the term probiotic, investigators should refer specifically to the actual organism being tested for putative beneficial effects. For example, some but not all organisms tested for probiotic activity have reported benefits in irritable bowel syndrome.[3] Most of the organisms tested in the recent meta-analysis of IBD never actually qualified for the stated definition: a health benefit when provided in adequate amounts. Activity in vitro or improvement of animal models is not the same as clinical benefit, and where benefit has been claimed, dosimetry has seldom been tested. Disappointing results observed in humans with seemingly beneficial microbes are in striking contrast to reported benefits in experimental animals. Is this because rodent models do not reflect the heterogeneity of human IBD? Host–microbe interactions in rodents inbred and raised in captivity may be too limited to reflect the complexity of what occurs in outbred humans.

Although the candidate probiotics tested in IBD seem to be extensive and diverse, they are, in fact, from a relatively narrow range of organisms, mainly *Lactobacillus* spp. and *Bifidobacteria* spp. and occasionally *Saccharomyces* and *Escherichia coli*. A new generation of species drawn from *Akkermansia*, *Bacteroides*, *Faecalobacterium* and others, are in development. These are operationally referred to as next-generation probiotics or live biotherapeutics.[4] They promise new benefits and challenges, but are likely to be developed as pharmaceuticals rather than supplements, and accordingly, will require a higher level of regulatory scrutiny.

Of course, abnormal host–microbe interactions are germane not only to the pathogenesis of IBD but also to the risk of extra-intestinal associations, manifestations, and complications including bacterial translocation, sepsis and progression to dysplasia or carcinogenesis.[3] The role for first- and next-generation probiotics or other microbial-based interventions for these aspects of the disease remains to be assessed.

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Editorial: probiotics in inflammatory bowel disease—wrong organisms, wrong disease, or flawed concepts? Authors' reply

Professor Shanahan highlights many of the methodological limitations of trials of probiotics in inflammatory bowel disease (IBD), which we do not dispute. Our systematic review and meta-analysis provides a contemporaneous summary of all the available data from clinical trials of probiotics in IBD.[1] Nevertheless the implications of our findings pose several questions that are highlighted in the accompanying Editorial.[2]

Unlike in irritable bowel syndrome,[3] to date, randomised controlled trials (RCTs) assessing the effect of probiotics in IBD have been sparse. In addition, they have been conducted using a relatively small sample of bacterial species in heterogeneous patient